



# **Dengue Vaccine Evidence to Recommendations Framework**

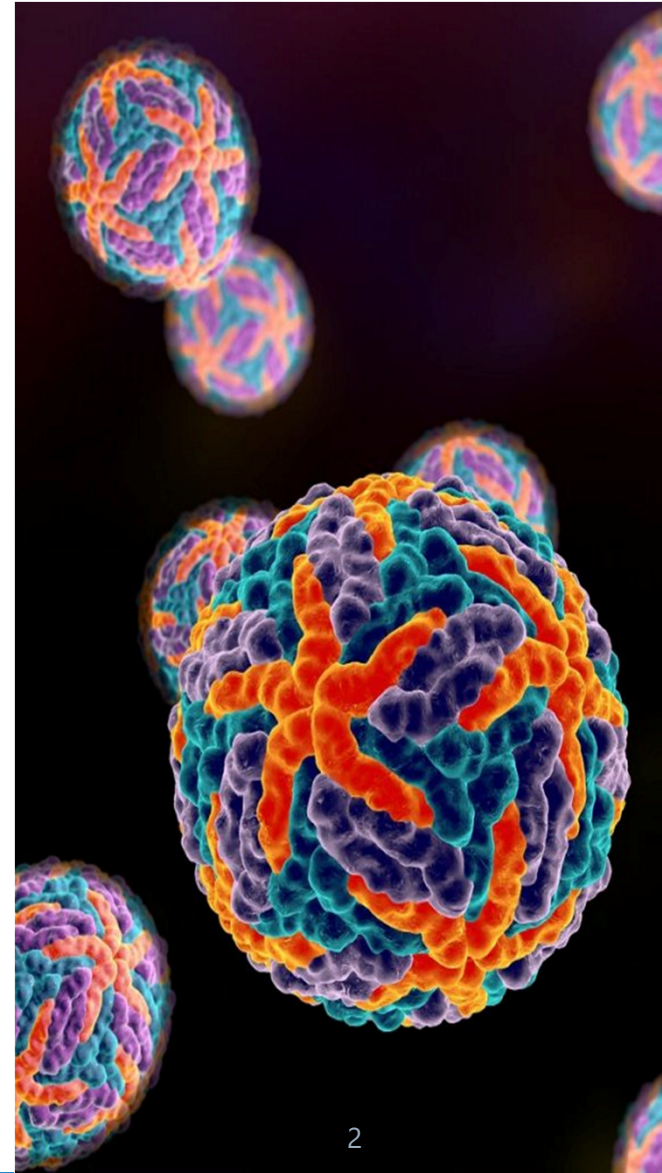
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**Dengue Branch, Division of Vector-Borne Diseases, CDC**

**ACIP, June 24, 2021**

# Dengue

- DENV-1, 2, 3, 4
  - Lifelong DENV type-specific immunity
  - Short-term cross-immunity
- Transmitted by the *Aedes* mosquitoes
- Most frequent arboviral disease globally



# Dengvaxia timeline

2015

- Trial results showed increased risk of severe disease among 2-5 year-olds

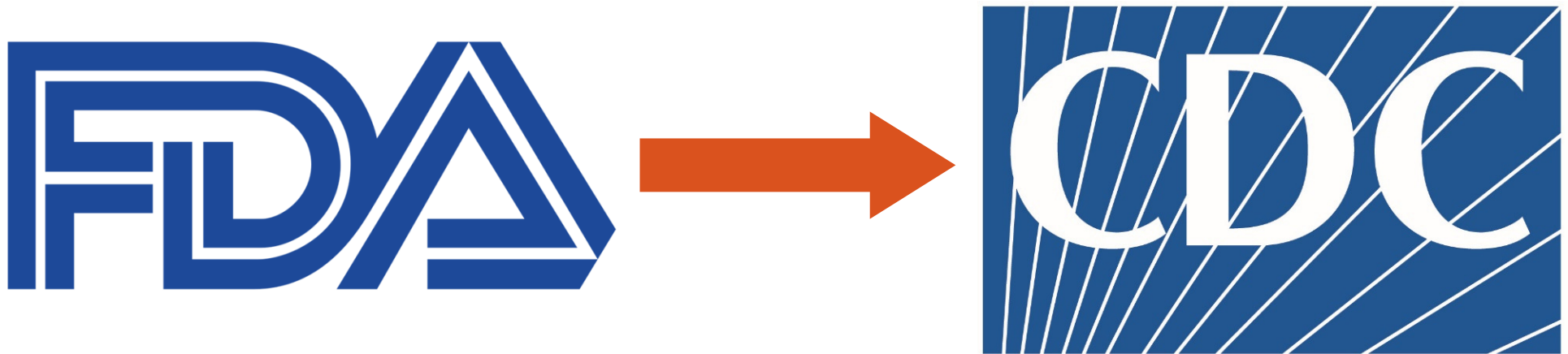
2016

- WHO position paper: 9y and older in highly endemic areas

2017

- Additional testing showed increased risk of severe dengue and hospitalization among vaccinated seronegative children compared to controls
- WHO revised their recommendations vaccine should only be given to children with laboratory-confirmed evidence of a past infection.

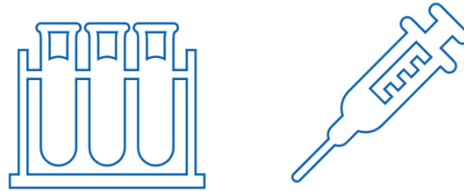
# FDA Licensing of first dengue vaccine 2019



For use in U.S. children 9-16 years old with laboratory-confirmed previous dengue virus infection and living in an area where dengue is endemic.

# Test performance guidance for pre-vaccination screening

■ 98% specific



■ 75% sensitive

■ 90% positive predictive value

■ 75% negative predictive value



# CDC evaluation of dengue virus IgG tests

Test	Sensitivity % (95% CI) DENV N=22	Specificity % (95% CI) NEG + ZIKV N=85
ELISA test 2	68 (45, 86)	97 (90, 99)
Rapid test 3a	82 (60, 95)	98 (92, 100)
Rapid test 3b	68 (45, 86)	98 (92, 100)

Dr. Freddy Medina, CDC, personal communication

# Evidence to Recommendations Framework



# Evidence to Recommendations (EtR) Framework

EtR Domain	Question
Public Health Problem	<ul style="list-style-type: none"><li>• Is the problem (<i>Dengue</i>) of public health importance?</li></ul>
Benefits and Harms	<ul style="list-style-type: none"><li>• How substantial are the desirable anticipated effects of the intervention (<i>dengue vaccine</i>)?</li><li>• How substantial are the undesirable anticipated effects?</li><li>• Do the desirable effects outweigh the undesirable effects?</li></ul>
Values	<ul style="list-style-type: none"><li>• Does the target population feel the desirable effects are large relative to the undesirable effects?</li><li>• Is there important variability in how patients value the outcomes?</li></ul>
Acceptability	<ul style="list-style-type: none"><li>• Is the intervention acceptable to key stakeholders?</li></ul>
Feasibility	<ul style="list-style-type: none"><li>• Is the intervention feasible to implement?</li></ul>
Resource Use	<ul style="list-style-type: none"><li>• Is the intervention a reasonable and efficient allocation of resources?</li></ul>
Equity	<ul style="list-style-type: none"><li>• What would be the impact of the intervention on health equity?</li></ul>



# Policy Question

**Question:** Should 3-doses of Dengvaxia be administered routinely to persons 9-16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?

# Public Health Problem

Is dengue disease of public health importance?

☐ No   ☐ Probably no   ☐ Probably yes   ☐ Yes   ☐ Varies   ☐ Don't know



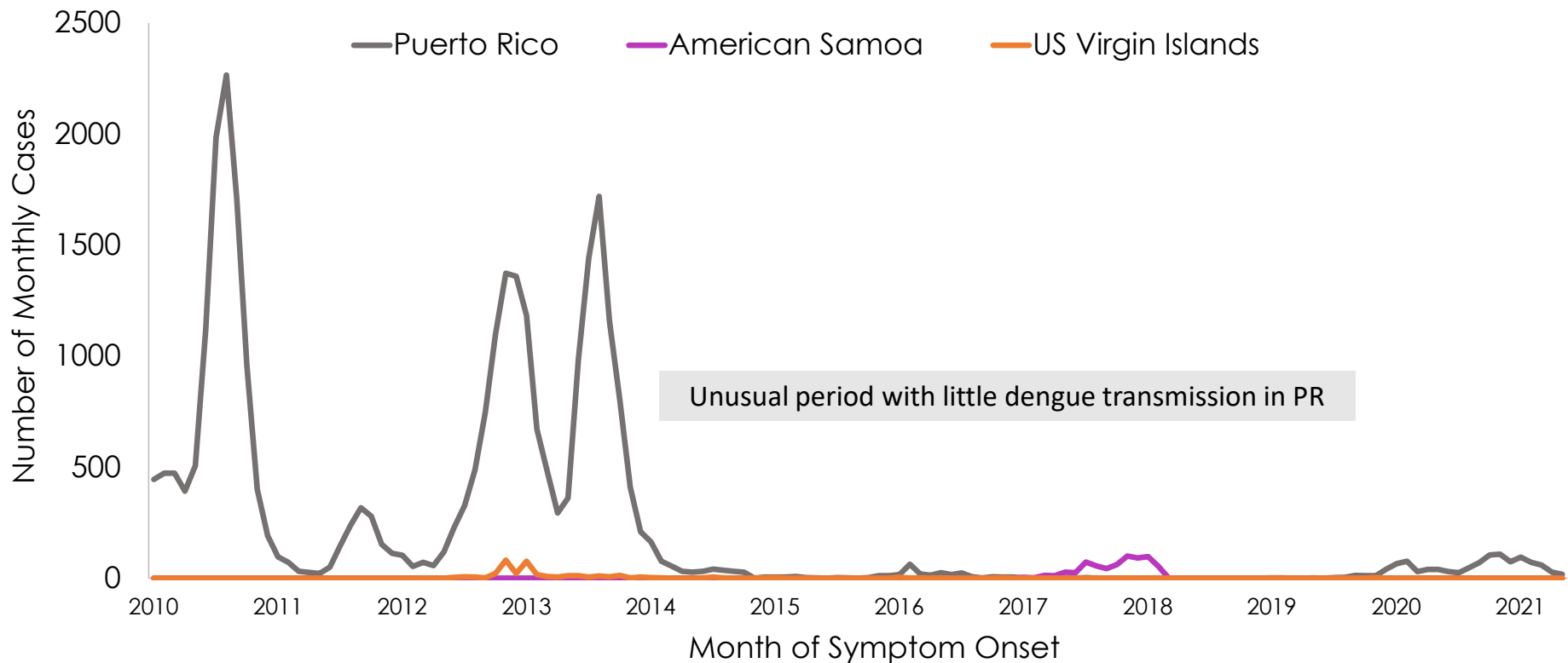
# Dengue endemic areas in the United States

85% of the children to be vaccinated are in Puerto Rico

Territory/Associated State	Population 9-16 years (2019)	%
Puerto Rico	303,826	85%
US Virgin Islands	12,000	3%
American Samoa	10,100	3%
Federated States of Micronesia*	16,000	4%
Palau*	2,423	1%
Marshall Islands*	14,000	4%

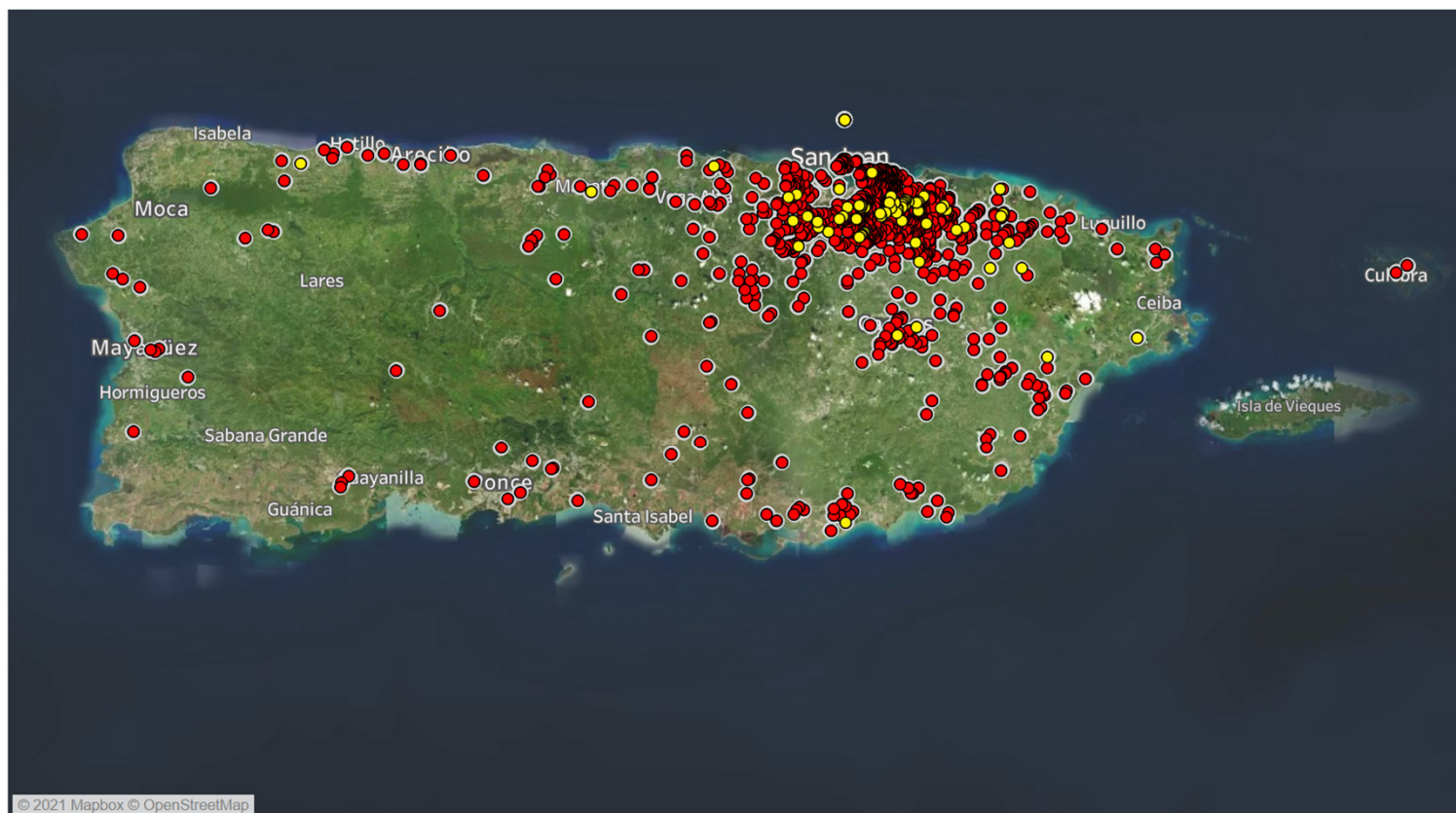
\*Sovereign freely associated states

# 95% of dengue cases in U.S. territories occur in Puerto Rico



Source: Dengue cases in ArboNET, Jan 2010–May 2021. Case counts from 2020 and 2021 are preliminary and subject to change.

# Dengue confirmed cases in Puerto Rico 2020-2021



Total cases Nov 2019-Jun 2021: 1,239

Legend    ■ Apr/May/Jun 2021    ■ Earlier

Source: Dengue passive surveillance system, Jan 2020–May 2021. Case counts from 2020 and 2021 are preliminary and subject to change. Reproduced with permission from Jomil Torres.

# Dengue seroprevalence in Puerto Rico

- Argüello et al: 10-18 years<sup>1</sup>
  - 2007 (n=345): 50% (95% CI: 44–56)
- Sanofi Pasteur trial data: 9-16 years<sup>2</sup>
  - 2011 (n=152): 56% (95% CI: 47–64)
- COPA project<sup>3</sup>: 9-16 years, DENV PRNT>10
  - 2018 (n=414): 59% (95% CI: 54–63)

1. Argüello DF, et al. AJTMH. 2015 Mar 4;92(3):486-91.

2. L'Azou M, et al. TRSTMH. 2018 Apr 1;112(4):158-68.

3. Unpublished.

# Public Health Problem:

## Work Group Interpretation

Is dengue disease of public health importance?

☐ No    ☐ Probably no    ☐ Probably Yes    ☒ Yes    ☐ Varies    ☐ Don't know



# Benefits and Harms

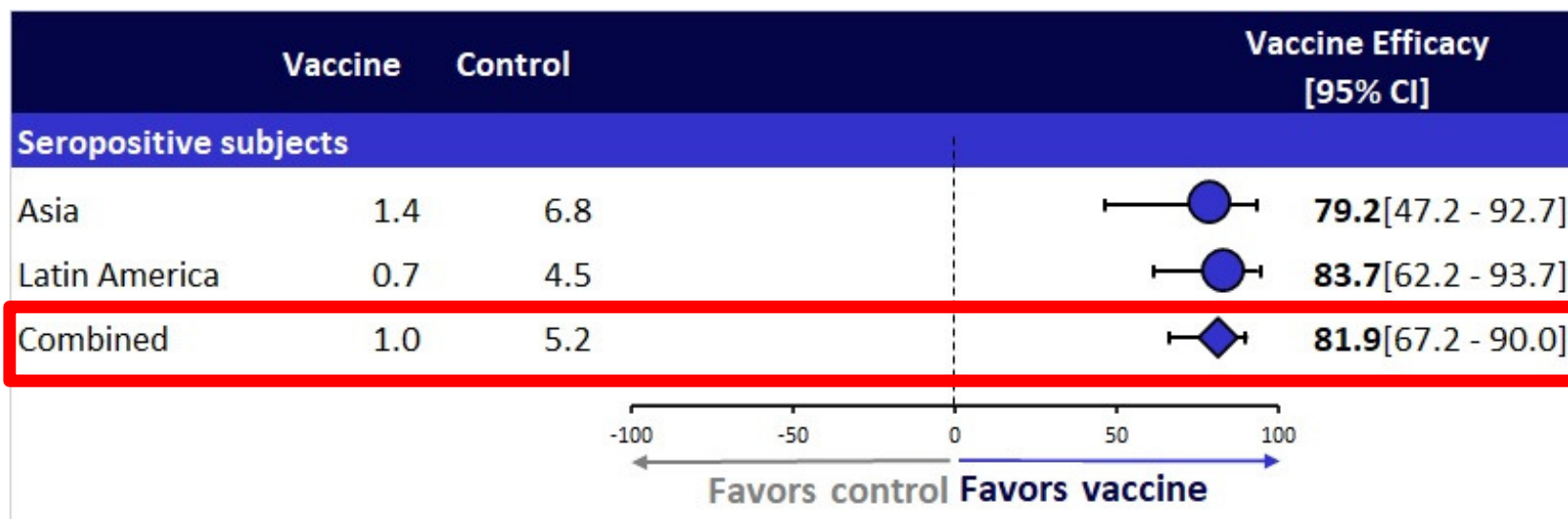
How substantial are the desirable anticipated effects?

☐ Minimal   ☐ Small   ☐ Moderate   ☐ Large   ☐ Varies   ☐ Don't know



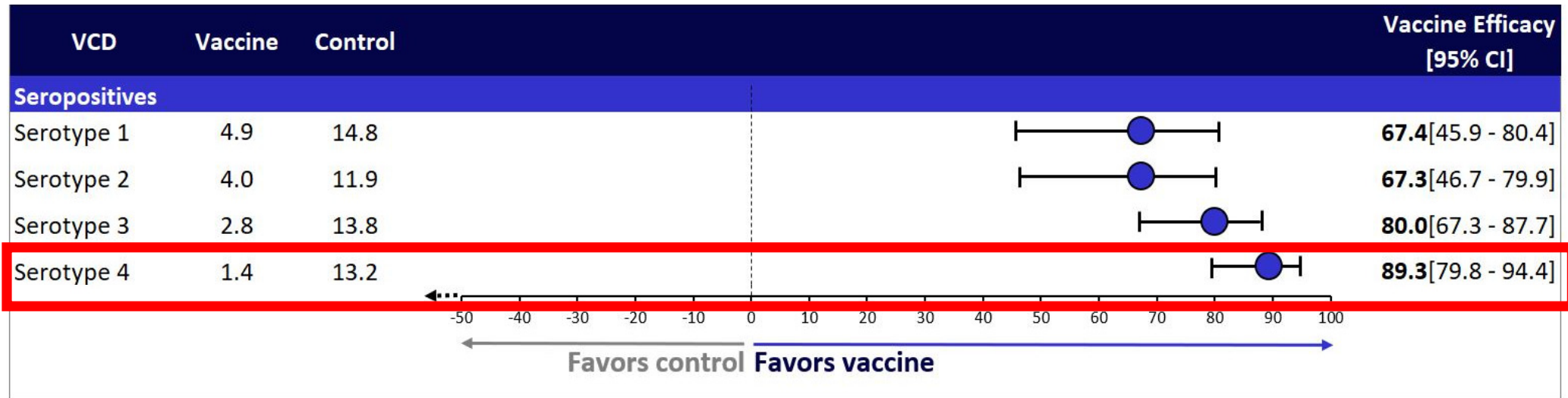


# Efficacy virologically confirmed dengue (VCD) at 25 months, seropositive participants 9-16 years



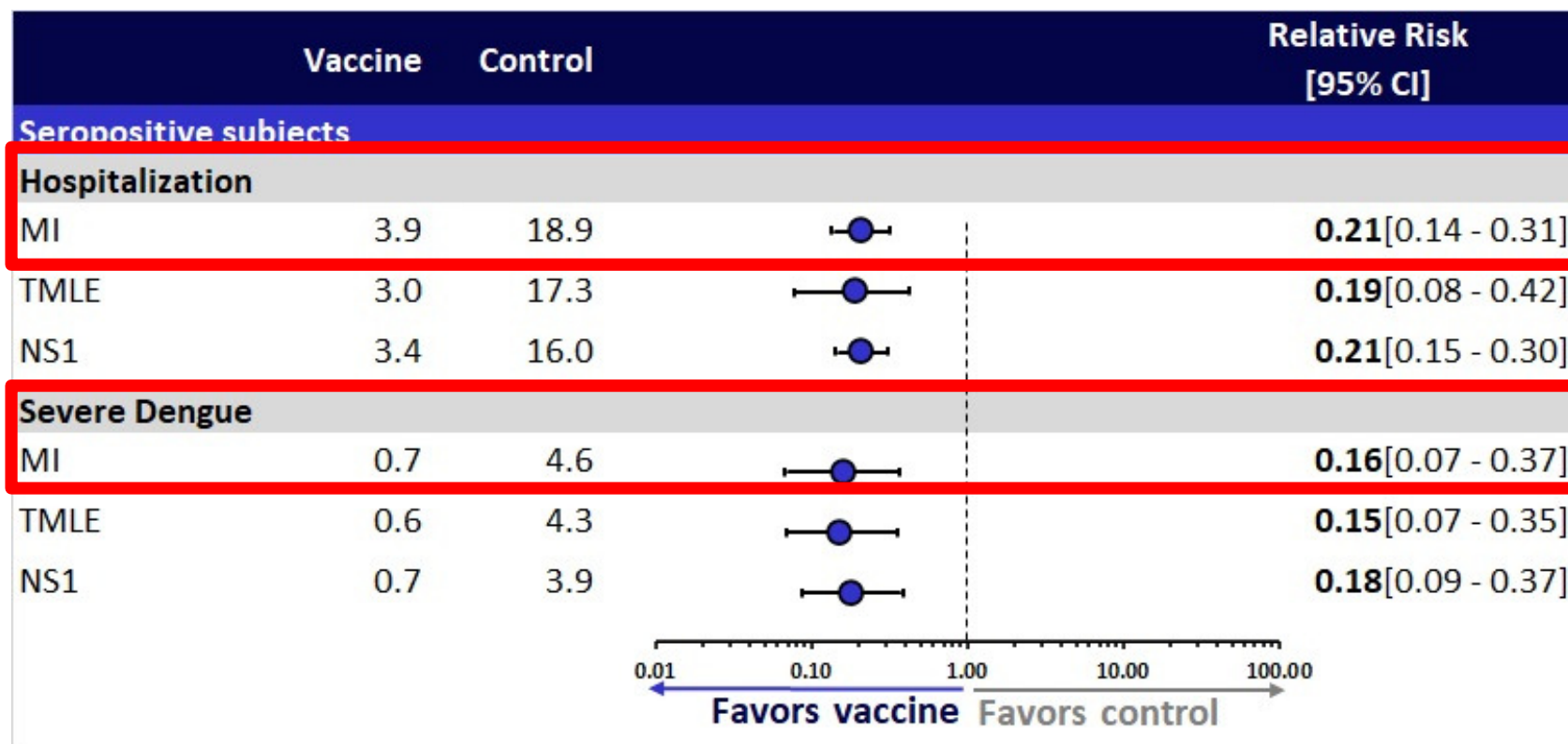
Hadinegoro SR et al. N Engl J Med 2015;373:1195-1206.

# Efficacy against VCD by serotype, seropositive participants 9-16 years



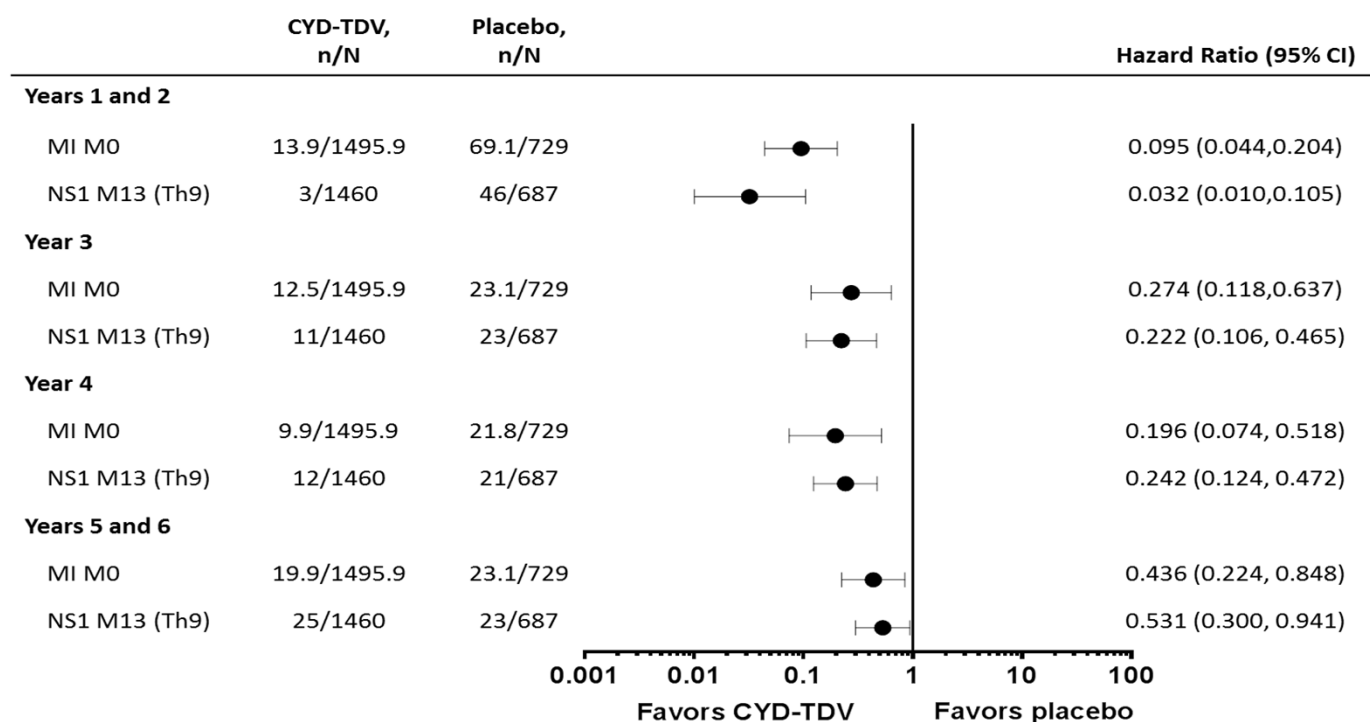
Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

# Efficacy against hospitalization and severe dengue at 60 months, seropositive participants 9-16 years



Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

# Risk of dengue hospitalization for each time period over 6-years, seropositive participants 9–16 year



Forrat R et al. CID 2021.

# How substantial are the desirable anticipated effects?

☐ Minimal   ☐ Small   ☒ Moderate   ☐ Large   ☐ Varies   ☐ Don't know

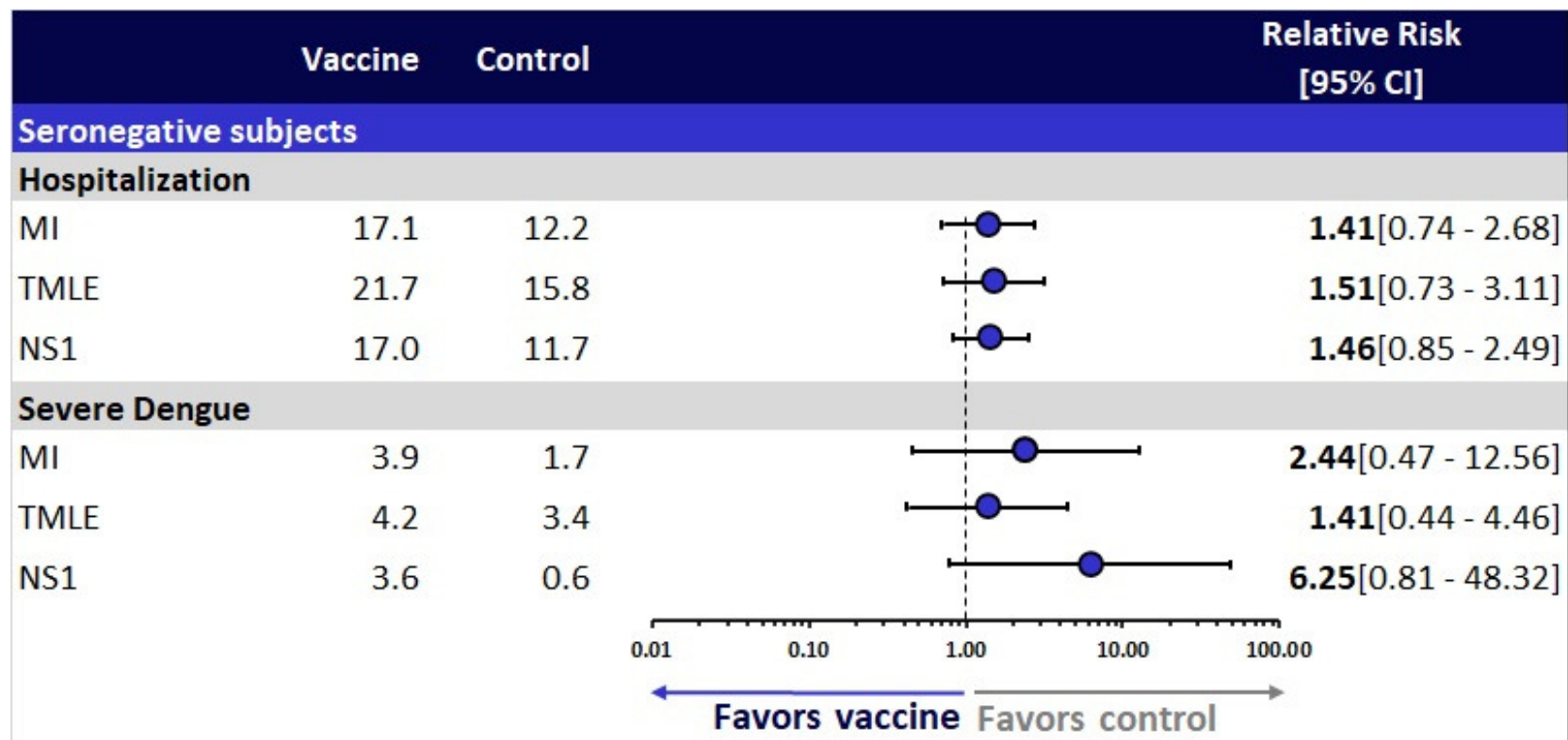


How substantial are the undesirable anticipated effects?

☐ Minimal   ☐ Small   ☐ Moderate   ☐ Large   ☐ Varies   ☐ Don't know

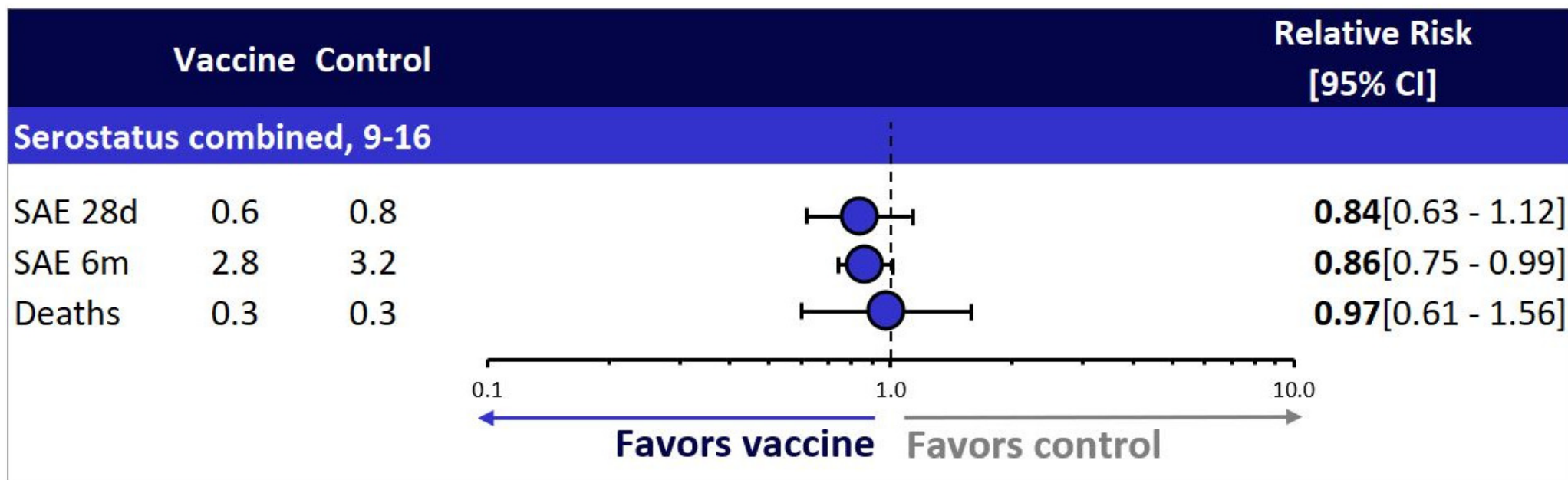


# Risk of hospitalization and severe dengue at 60 months, seronegative participants 9-16 years



Sridhar, S, et al. N Engl J Med. 2018 Jul 26; 379(4):327-340

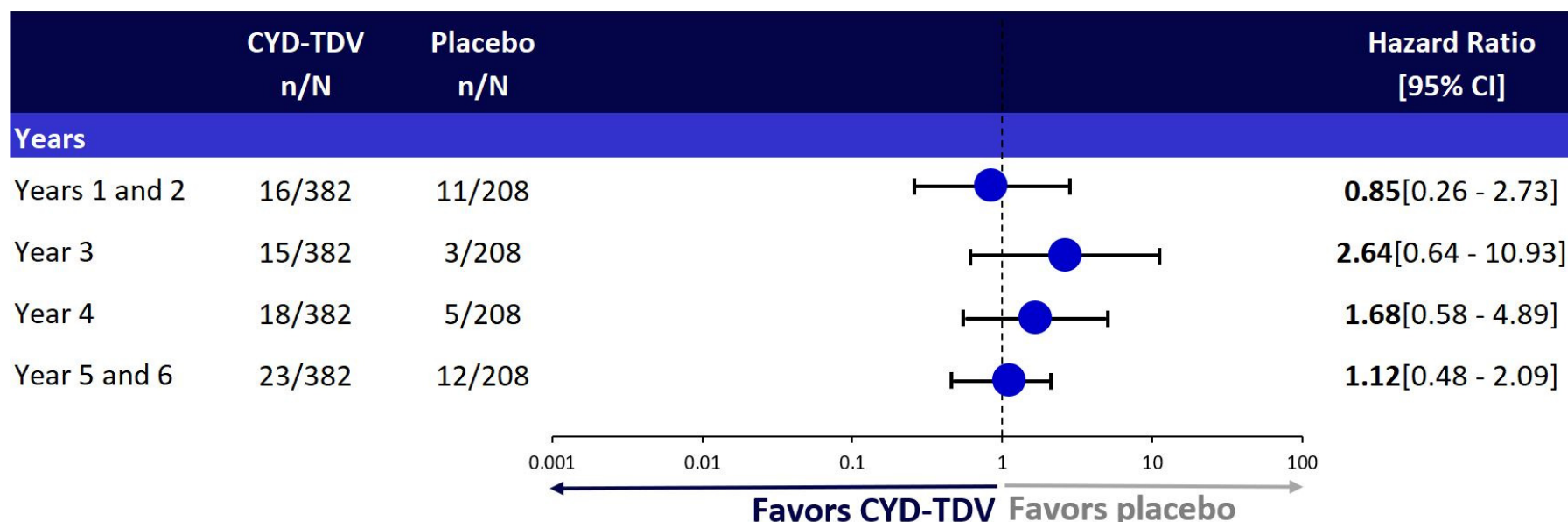
# Severe adverse events and deaths among participants 9-16 years, serostatus combined



Gustavo Dayan, Sanofi, personal communication.



# Risk of dengue hospitalization for each time period over 6 years, seronegative participants ages 9–16 years



Multiple imputation

Sanofi Pasteur, personal communication, March 15, 2021

# How substantial are the undesirable anticipated effects?

☐ Minimal ☒ Small ☐ Moderate ☐ Large ☐ Varies ☐ Don't know



# Do the desirable effects outweigh the undesirable effects?

- ☐ Favors intervention
- ☐ Favors comparison
- ☐ Favors both
- ☐ Favors neither
- ☐ Varies
- ☐ Don't know



# Benefits and harms

- **Benefits of Dengvaxia**

- Efficacy against symptomatic virologically confirmed dengue (82%, CI: 67-90)
- Efficacy against dengue hospitalizations (79%, CI: 69-86)
- Efficacy against severe dengue (84%, CI: 63-93)

- **Harms of Dengvaxia**

- Increased risk of vaccine-induced hospitalization if a seronegative child is vaccinated after a false-positive laboratory test

# Population impact of screen and vaccinate strategy

- Agent-based model of dengue transmission with humans and mosquitoes represented as agents
- Calibrated to simulate dengue transmission in Puerto Rico
- Compares pre-vaccination screening and subsequent vaccination of seropositive 9-year-olds to the status quo
- Model population followed for 10 years keeping track of dengue infections, hospitalizations and deaths
- Prevalence at age 9 years of age of 50% and 30%
- Population level benefits: symptomatic and hospitalized cases averted
- Risks: vaccine –induced hospitalizations among dengue-naïve individuals

# Population-level impacts of the intervention in Puerto Rico

Total numbers of symptomatic and hospitalized cases as well as cases averted and additional hospitalizations among vaccinees.

Time frame modeled: 10 years

Strategy: testing and vaccinating cohorts of test-positive 9-year-old children in Puerto Rico annually

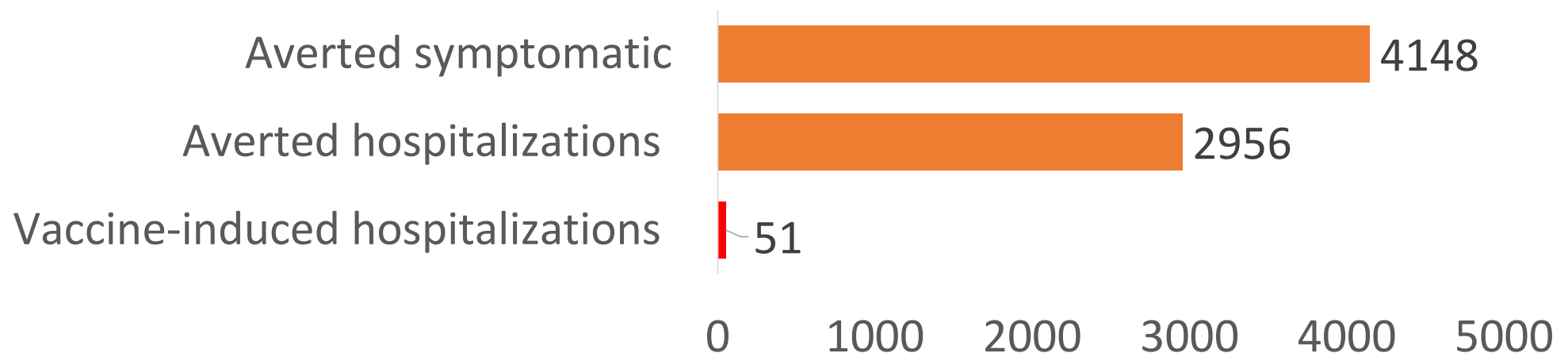
Test performance: sensitivity = 0.75 and specificity = 0.98.

	Baseline		Test and vaccinate strategy		Averted		Additional	Ratio
Prior exposure in 9-yr-olds	Symptomatic	Hospitalizations	Tested	Vaccinated	Symptomatic	Hospitalizations	Hospitalizations	averted/additional
30%	221751	51278	317823	61825	1551	1262	112	11/1
50%	260218	60663	317814	102884	4148	2956	51	57/1
60%	271711	63807	317809	125127	5538	4295	28	152/1

# Benefits and harms of vaccination among a 10-year cohort of 9-year-old children 50% seroprevalence

Screening test 75% sensitive and 98% specific

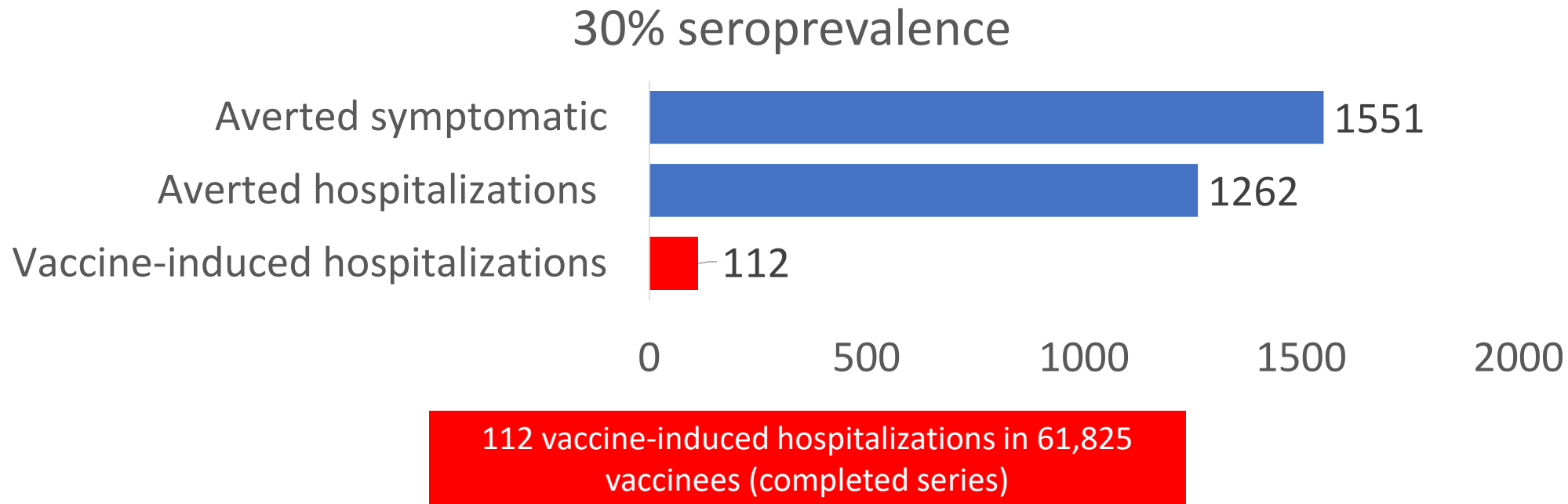
50% seroprevalence



51 vaccine-induced hospitalizations in  
102,884 vaccinees (completed series)

# Benefits and harms of vaccination among a 10-year cohort of 9-year-old children 30% seroprevalence

Screening test 75% sensitive and 98% specific





# Summary of population benefits and harms of vaccination among a 10-year cohort of 9-year-old children

## 50% seroprevalence

- Risks
  - 51 vaccine-induced hospitalizations among seronegative children
- Benefits
  - 4148 fewer symptomatic cases
  - 2956 fewer hospitalizations

## 30% seroprevalence

- Risks
  - 112 vaccine-induced hospitalizations among seronegative children
- Benefits
  - 1551 fewer symptomatic cases
  - 1262 fewer hospitalizations

## **Interpretation benefits and harms**

- Shows positive balance for benefits versus harms
- Balance of risk and benefits varies by seroprevalence

# Do the desirable effects outweigh the undesirable effects?

☒ Favors intervention

☐ Favors comparison

☐ Favors both

☐ Favors neither

☐ Varies

☐ Don't know



# What is the overall certainty of the evidence?

## Effectiveness of the intervention

☐ 4 (very low)   ☐ 3 (low)   ☐ 2 (moderate)   ☒ 1 (high)

## Safety of the intervention

☐ 4 (very low)   ☐ 3 (low)   ☒ 2 (moderate)   ☐ 1 (high)



# Values

Does the target population feel that the desirable effects are large relative to undesirable effects?

☐ No   ☐ Probably no   ☒ Probably Yes   ☐ Yes   ☐ Varies   ☐ Don't know



# Is there important uncertainty about or variability in how much people value the main outcomes?

- Important uncertainty or variability
- Probably important uncertainty or variability
- Probably not important uncertainty or variability
- Not important uncertainty or variability
- No known undesirable outcomes



# Acceptability

Is the intervention acceptable to key stakeholders?

☐ No   ☐ Probably no   ☒ Probably Yes   ☐ Yes   ☐ Varies   ☐ Don't know



# Feasibility

Is the intervention feasible to implement?

☐ No    ☐ Probably no    ☐ Probably Yes    ☐ Yes    ☐ Varies    ☐ Don't know





# Feasibility assessment has focused in PR due to burden, lessons learned will help prepare

Territory/Associated State	Population 9-16 years (2019)	%	Vaccine providers	Laboratories
Puerto Rico	303,826	85%	505	450
US Virgin Islands	12,000	3%	11	8
American Samoa	10,100	3%	4	1
Federated States of Micronesia*	16,000	4%	2	2
Palau*	2,423	1%	4	1
Marshall Islands*	14,000	4%	2	2

\*Sovereign freely associated states

## **USVI survey of healthcare facilities (n=11)**

- 4/11 were aware there was an FDA approved vaccine
- 5/11 would recommend the vaccine if there was a test available for screening
- 7/11 need more information before recommending it

# Pacific Islands

- Presentation on Dengvaxia to PIHOA
- Planning a survey of providers by University of Georgia
- Partnership to test left over samples of household-based surveys to determine dengue seroprevalence

# Is the intervention feasible to implement?

☐ No   ☐ Probably no   ☒ Probably Yes   ☐ Yes   ☐ Varies   ☐ Don't know



# Resource Use

**Is the intervention a reasonable and efficient allocation of resources?**

☐ No    ☐ Probably no    ☐ Probably Yes    ☐ Yes    ☐ Varies    ☐ Don't know



# Cost-effectiveness analyses of Dengvaxia use in Puerto Rico 2019 Costs

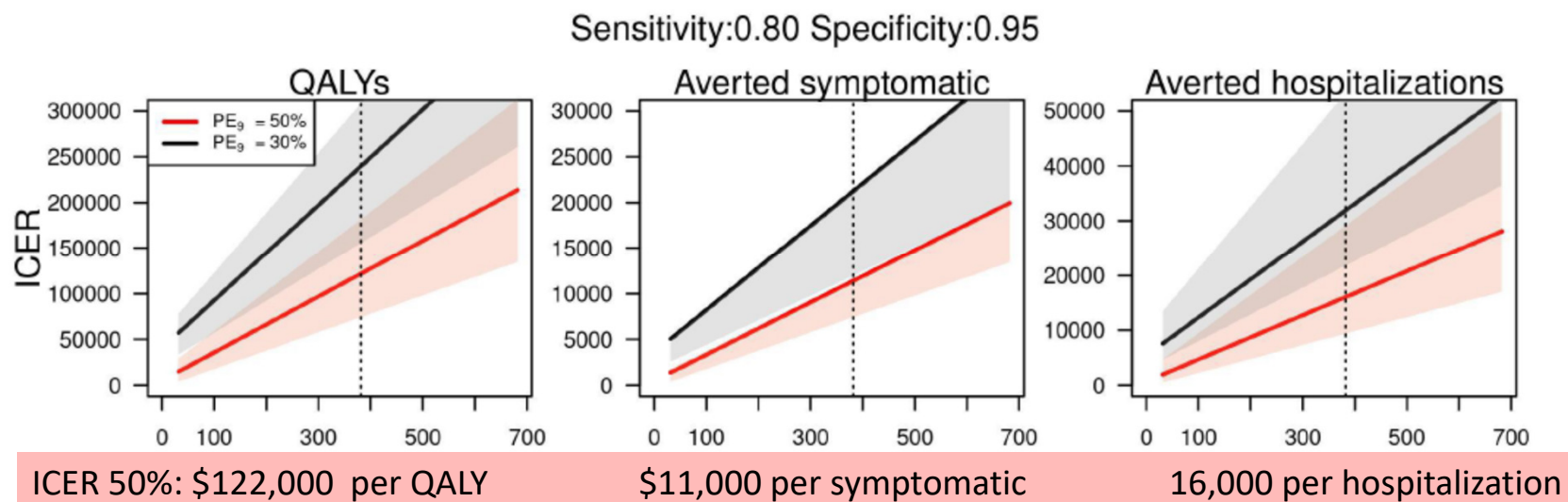


Figure 5. ICER of pre-vaccination screening strategy in Puerto Rico at different costs of vaccination (total cost for three doses per person), assuming a unit cost of serological screening of 30 USD. Dotted line represents the baseline assumption of vaccine cost (382 USD). All costs in 2019 USD.

- Espana G, Leidner A, Waterman S, Perkins A. Cost-effectiveness of Dengue Vaccination in Puerto Rico. <https://www.medrxiv.org/content/10.1101/2020.10.07.20208512v1>

# Is the intervention a reasonable and efficient allocation of resources?

☐ No   ☐ Probably no   ☒ Probably Yes   ☐ Yes   ☐ Varies   ☐ Don't know



# Equity

What would be the impact on health equity?

☐ Reduced   ☐ Probably reduced   ☐ Probably no impact   ☒ Probably increased   ☐ Increased   ☐ Varies   ☐ Don't know





# Balance of consequences

- Undesirable consequences *clearly outweigh* desirable consequences in most settings
- Undesirable consequences *probably outweigh* desirable consequences in most settings
- The balance between desirable and undesirable consequences is *closely balanced or uncertain*
- Desirable consequences *probably outweigh* undesirable consequences in most settings
- Desirable consequences *clearly outweigh* undesirable consequences in most settings
- There is insufficient evidence to determine the balance of consequences



Is there sufficient information to move forward with a recommendation?

☒ Yes

☐ No



# Policy options for ACIP

- ACIP does not recommend the intervention (Intervention may be used within FDA licensed indications)
- ACIP recommends the intervention for individuals based on shared clinical decision-making
- ACIP recommends the intervention



# Option 1: ACIP does not recommend

## Cons

- A vaccine proven to protect persons with prior dengue infection will not be available to US citizens
- Puts off making difficult decision that may be needed for the next dengue vaccine approved by FDA

## Pros

- Avoids a complicated implementation in the middle of COVID vaccinations programs

## Option 2: Shared decision making

### Cons

- Lower uptake
- Little progress in sorting out feasibility
- Coverage of test by insurance companies challenging
- May increase health inequities due to unequal health literacy
- Less buy-in for large scale education and communication

### Pros

- Would lessen fears that the vaccine will become controversial and result in increased vaccine hesitancy

# Option 3: Routine recommendation

## Cons

- Public and media perception of the risks associated with the vaccine may increase vaccine hesitancy
- Potential public and provider perception that all hospitalizations among vaccinees related to vaccine

## Pros

- Effective vaccine for seropositive children
- Greater coverage, reduction in hospitalizations
- Better buy-in from health department and immunization program to resolve challenges with feasibility
- Broader communication and media campaign
- Increase in health equity

# Policy options for ACIP consideration

- ACIP does not recommend the intervention (Intervention may be used within FDA licensed indications)
- ACIP recommends the intervention for individuals based on shared clinical decision-making
- ACIP recommends the intervention



# Draft Recommendation

- ACIP recommends 3-doses of Dengvaxia administered 6 months apart at month 0, 6, and 12, in persons 9-16 years of age with a laboratory confirmation of previous dengue infection and living in endemic areas.



# ACIP Dengue Vaccines Workgroup

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